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ABSTRACT

Background: As COVID-19 overwhelms health systems worldwide, palliative care strategies may ensure rational use of resources while safeguarding patient comfort and dignity.

Aim: To describe palliative care practices in hospitalized middle-aged and older adults in two of the largest COVID-19 treatment centers in Sao Paulo, Brazil.

Design: Retrospective cohort

Setting/participants: Eligible patients were those aged 50 years or older hospitalized between March and May 2020 with a laboratory confirmation of SARS-CoV-2 infection. Palliative care implementation was defined as present if medical notes indicated a decision to limit escalation of life support measures, or when opioids or sedatives were prescribed for palliative management of symptoms.

Results: We included 1162 participants (57% male, median 65 years). Overall, 21% were frail and 54% were treated in intensive care units, but only 17% received palliative care. Stepwise logistic regression demonstrated that age ≥80 years, dementia, history of stroke or cancer, frailty, having a $PaO_2/FiO_2<200$ or a C-reactive protein ≥150mg/dl at admission predicted palliative care implementation. Patients placed under palliative care stayed longer (13 vs.11 days) and were more likely to die in hospital (86 vs.27%). They also spent more days in ICU and received vasoactive drugs, hemodialysis, and invasive ventilation more frequently.

Conclusions: one in five middle-aged and older adults hospitalized with COVID-19 received palliative care in our cohort. Patients who were very old, multimorbid, frail, and had severe COVID-19 were more likely to receive palliative care. However, it was often delayed until advanced and invasive life support measures had already been implemented.

Key words: COVID-19, Palliative care, health care rationing

Key message statement: In this retrospective cohort, one in five middle-aged and older adults hospitalized with COVID-19 received palliative care. Patients who were very old, multimorbid, frail, and had severe COVID-19 were more likely to receive palliative care, but it was often delayed until advanced life support measures had already been implemented.

Conflict of interest statement: The authors have no conflict of interest to declare

1. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China in 2020 following an unexplained outbreak of pneumonia in the province of Wuhan (1). The disease, subsequently named COVID-19, is a potentially life-threatening inflammatory disorder that frequently manifests with respiratory symptoms and may progress to acute respiratory distress syndrome and death (2).

COVID-19 was declared a pandemic on March 11th, 2020, and, despite major efforts to contain the spread of the virus, it has infected more than 180 million and killed 4 million people worldwide as of July 1st, 2021 (3). While substantial investments in therapeutic and vaccine research were made in 2020, most countries had to adopt social distancing measures to prevent their healthcare systems from collapsing. With most of the world yet to be immunized, and the alternate tightening and loosening of social distancing recommendations, new waves of COVID-19 cases have been a recurring phenomenon in 2021.

Such outbreaks expose how healthcare systems are still vulnerable to the pandemic. In countries like Brazil and India, new SARS-CoV-2 variants have emerged to overwhelm public and private hospitals (4). The combination of increased infectivity and virulence, slow vaccine rollout, and political ineptitude have resulted in hospital beds shortages and numerous deaths (5). In such dramatic scenarios, front-line providers have been repeatedly challenged with having to decide on how to allocate available resources.

Palliative care is widely accepted as critical to ensuring rational use of resources while safeguarding patient comfort and dignity. Consequently, palliative care strategies are particularly relevant during a crisis like the COVID-19 pandemic (6-8). However, it is important to understand the real-life context in which these strategies are implemented and who benefits the most from them. Therefore, we aimed to describe palliative care practices in hospitalized middle-aged and older adults with COVID-19 in two of the largest COVID-19 treatment centers in Sao Paulo, Brazil. We further investigated predictors of palliative care and its association with intensive care admission and length of hospital stay.

2. METHODS

2.1. Study design and participating centers

We completed a retrospective cohort study in two major teaching hospitals in Sao Paulo, Brazil, converted to COVID-19 treatment centers in 2020. Hospital Municipal Dr. Moyses Deutsch (Hospital 1) is a secondary community hospital serving approximately 1 million people; Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (Hospital 2) is a tertiary public hospital and referral center for sub-specialty services for the State of Sao Paulo. Both hospitals have long-standing traditions in medical education, with students, residents, and fellows remaining actively engaged in patient care during the COVID-19 pandemic.

As occurred in many parts of Brazil and around the globe, both hospitals underwent major adaptations to meet the sudden increase in demand. These included changes in processes, infrastructure, medical and human resources which had to be put in place at a record amount of time. As such, non-COVID patients were transferred in order to avoid in-hospital contamination, the number of ward and ICU beds were significantly increased, and more healthcare professionals were hired(9). Palliative care teams comprised of specialized physicians in hospital 1 and a multidisciplinary team in hospital 2 were also expanded, but pre-pandemic eligibility criteria and treatment protocols were maintained.

The study was approved by the local institutional review boards at each site (CAAE: 34661520.5.0000.0086).

2.2. Eligibility criteria and data collection

We identified all consecutive hospital admissions for COVID-19 between March and May 2020. This period corresponded to the exponential increase in the number of COVID-19 cases and hospitalizations in the metropolitan area of Sao Paulo during the first wave of the pandemic. Eligible patients were 50 years or older and had laboratory confirmation of SARS-CoV-2 infection. We excluded candidates discharged from the emergency department, hospitalized for less than 24 hours, and those with missing data on our main variables.

We reviewed hospital medical records for demographic, clinical, laboratory, and imaging data on our participants. We also collected data on medical history, pre-COVID-19 frailty status (Clinical Frailty Scale)(10), disease severity on admission, ventilatory and

hemodynamic support during hospital stay, intensive care admission, length of hospital stay, and death.

We assessed whether participants were placed under palliative care during hospitalization. Palliative care implementation was defined as present when medical notes explicitly described so, including the planning of goals of care, the decision to limit the escalation of life support measures and communicating with patients and their families, or when opioids or sedatives were prescribed for the management of distressing symptoms. In our subset of participants from Hospital 1, we were also able to determine the moment and setting of palliative care recommendations and the reasons for their indication according to best practices guidelines (11, 12). Importantly, the decision to initiate palliative care was always made together by the attending physician and the patient or his/her proxy, with follow-up by the specialized palliative care team being strongly recommended, but not mandatory. Attending physicians in wards and intensive care units were permitted to manage those patients without the assistance of the palliative care team if they felt confident about their skills to do so.

Our main outcomes were palliative care implementation (yes/no), intensive care admission, and length of hospital stay.

2.3. Statistical Analysis

Descriptive results for the total sample are reported, comparing the variables of interest according to study site. Chi-square test was used to compare categorical variables, and Student's t-test (normal distribution) or Wilcoxon's rank-sum test (non-normal distribution) for numerical variables.

We selected 20 variables to feed our palliative care prediction model, based on their clinical relevance and causal relations: age, sex, asthma, chronic pulmonary obstructive disease (COPD), obesity, diabetes, hypertension, heart failure, coronary disease, cerebrovascular disease, chronic kidney disease, cancer, HIV infection, frailty, length of COVID-19 symptoms, invasive ventilation, admission PaO_2/FiO_2 ratio, lymphocytes, and C-reactive protein. Subsequently, we explored the association between each variable of interest and palliative care in univariable logistic regressions and used stepwise logistic regression models to identify independent predictors of palliative care.

All statistical tests were two-tailed, with a significance level set at 0.05. The analyses were conducted using Stata (version 15.1, StataCorp, College Station, TX).

3. RESULTS

We included 1162 participants, 392 from Hospital 1 and 770 from Hospital 2, from all regions of the Sao Paulo metropolitan area (Figure 1). They were predominantly male (57%), and the median age was 65 years. The most common comorbidities were hypertension (71%), diabetes (47%), and obesity (32%). Overall, 21% were classified as frail (Table 1).

The median duration of symptoms on admission was seven days. Participants from Hospital 2 were hospitalized sooner from the onset of symptoms. As expected for a tertiary hospital, they also showed signs of greater disease severity on admission, as indicated by lower PaO_2/FiO_2 ratios and lymphocyte counts, and a greater proportion of patients using invasive ventilation (Table 1).

Overall, 54% of our sample required intensive care, 20% used vasoactive drugs, and 21% underwent hemodialysis at some point during hospital stay. The median length of hospital stay was 11 days, and in-hospital mortality reached 37%. Participants from Hospital 2 used invasive mechanical ventilation and renal replacement therapy more frequently during hospitalization. Likewise, they stayed in the hospital longer and had higher mortality (Table 1).

3.1. Palliative care predictors and outcomes

A total of 198 (17%) participants were placed on palliative care, 73 (19%) in Hospital 1 and 124 (16%) in Hospital 2. Palliative care patients were generally older, had more comorbidities (particularly chronic cardiopulmonary conditions, neurologic diseases, and cancer), and were more frequently frail. They also presented with greater disease severity on admission, as shown by their lower PaO_2/FiO_2 ratios, more extensive lung injuries, and a greater proportion of patients using invasive ventilation (Table 2).

After stepwise logistic regression analysis, we found that age ≥80 years, dementia, history of stroke, cancer, frailty, admission PaO_2/FiO_2 <200, and admission C-reactive protein ≥150 mg/dl were independent predictors of palliative care implementation (Table 3).

We observed that palliative care patients stayed longer (13 vs. 11 days) and were three times more likely to die in the hospital (86 vs. 27%). They also spent more days in intensive care and were more frequently treated with vasoactive drugs, hemodialysis, and invasive ventilation during hospital stay (Table 2).

3.2. Subgroup analyses of palliative care

Data from our Hospital 1 participants indicated that 98/392 would have been eligible for palliative care due to substantial multimorbidity or severe functional impairment, and 35/392 would have been eligible due to COVID-19 treatment failure. However, only 77/392 eventually received palliative care (58% of eligible patients). In this group, palliative care was justified by multimorbidity or functional impairment in 70% of the patients and treatment failure in 27.3%.

Overall, the median time between hospital admission and palliative care implementation was eight days (Table 4). Palliative care in patients with substantial multimorbidity or severe functional impairment started earlier than those with treatment failure (5 vs. 14 days after hospital admission). Multimorbid or dependent patients were also four times less likely to be in intensive care when palliative care was implemented when compared treatment failure patients (22.2% vs. 85.7%).

In Hospital 1, mortality reached 79% in palliative care patients, with a median time of two days between palliation and death (Table 4).

4. DISCUSSION

Main findings

This is the largest study to investigate palliative care in COVID-19 patients in Brazil. Our results showed that age, multimorbidity, frailty, and COVID-19 severity were independent predictors of palliative care. Nevertheless, data from a subset of our sample suggest that palliative care was often initiated late in the disease progression. Many of our patients experienced extended hospital stays, intensive care admissions, and invasive procedures before initiating palliative care measures.

In a pre-pandemic Brazilian cohort of 572 medical admissions of adults over the age of 60 years carried out in hospital 2, Arcanjo et al. found that male sex, cancer, advanced dementia, and low albumin levels were independently associated with palliative care referral(13). Conversely, we have examined patients aged 50 years or older, all admitted for COVID-19, and have identified additional predictors of palliative care including frailty, which has been recently associated with worse prognosis of COVID-19 (14).

Still, the results of our study suggest a very different palliative care practice in the two participating Brazilian centers compared to the international experience with COVID-19 patients described in previous reports. Two small cohorts from the United Kingdom (15, 16) reported a median time between hospital admission and palliative care referral of only 2 days and less than 10% of palliated patients having received intensive care support. On the other hand, 63% of palliated patients in our cohort received ICU treatment at some point during hospital stay and a subgroup analysis of patients admitted to hospital 1 revealed it took a median of 8 days for palliative care to be implemented. It is true that such discrepancies could be partly explained by demographic differences between the study samples, particularly when it comes to age and comorbidities, as palliated patients in our cohort were slightly younger and appeared to present less frequently with chronic comorbidities such as dementia or COPD. However, it was also noteworthy that patients eventually placed under palliative care in our cohort received invasive life support more frequently than those remaining on curative treatment and had longer hospital stay.

Taken together, these results could indicate that the reasons for palliation differed between our cohort and the previous ones, with more patients in our study being placed under palliative care due to treatment failure rather than poor baseline functional status. Indeed, a report of palliative care service volume and patients' characteristics during the COVID-19 pandemic in New York demonstrated that time for referral for palliation among COVID-19 patients was longer than for non-COVID-19 patients(17). They also had longer hospital stay and were more frequently treated in intensive care units than COVID-19 negative patients, but unfortunately the authors do not disclose the reasons for palliative care in each group.

Implications:

It might have been more challenging for some providers to recommend palliative care in the context of an acute and largely unknown respiratory disease and, understandably, medical care and decisions were disrupted by the COVID-19 pandemic on many levels. Nevertheless, it is precisely during such a healthcare crisis that rational and legitimate

palliative care recommendations become critical. Yet, we observed that almost half the patients who would have been eligible for palliative care in hospital 1 were never assessed for this approach.

Unfortunately, palliative care is still frequently misunderstood as relevant only for terminally ill patients when it should be valued as an evidence-based patient-centered intervention that preserves quality of life and optimizes resource utilization (7, 18, 19). The timely identification of palliative care candidates is a foremost step in this process. Not surprisingly, several medical societies have issued guidance recommendations early in the pandemic to assist front-line physicians in this task (20).

With Brazil ranking among the countries with the highest number of COVID-19 cases and casualties(3), it would be of the utmost importance that healthcare providers were familiar with the concepts and eligibility criteria for palliative care, but, sadly, our study suggests that is often not the case. It must be noted that our cohort comprises patients treated in two teaching hospitals with dedicated palliative care groups, which in theory should represent "the best-case scenario" for appropriate palliative care practice. Still, assessment for palliative care was frequently delayed to a point when patients were already receiving advanced life support.

Having said that, simply having specialized palliative care teams may not be enough to guarantee the timely implementation of appropriate clinical practices, as decision-making and management remain largely dependent on attending physicians, especially in scenarios of system overload. Therefore, our data highlights the urgent need to improve physician knowledge and awareness about palliative care if we wish to achieve its individual and social benefits.

Limitations:

We completed a large cohort study and collected detailed information from middle-aged and older adults admitted for COVID-19 in secondary and tertiary hospitals. Still, our study had limitations. First, it reports retrospective analyses of data extracted from electronic medical records, which could be biased by poor documentation. Although research in palliative care has grown significantly in recent decades, the description of this patient population remains vague. In our study, we opted to capture clinical information that would most likely identify patients in palliative care. Previous studies have used similar strategies in the past(13, 21). Second, the two participating centers are traditional public teaching hospitals in Sao Paulo with established palliative care groups. Therefore, our results might not be

generalizable to other settings such as private or non-teaching hospitals without specialized palliative care teams, in which case it might be reasonable to assume timely recommendations for palliative care could be even less likely to happen. Third, given that this study was based on the retrospective analysis of electronic medical records and palliative treatment protocols were not necessarily homogeneous among centers, we opted to consider the implementation of palliative care as a dichotomous variable (yes/no) for the assessment of the primary outcome. The study design did not access palliative care indicators such as overall wellbeing/quality of life, decrease in dyspnea or pain, staff distress, information needs/preferences of the patients, or phase of chronic illness of each individual. Thus, the study does not allow us to draw any conclusions about the quality of palliative care assistance in either of the study sites. Finally, specific information about palliative care practice such as time to its implementation were available for only one of our study sites, further limiting generalizability.

5. CONCLUSION

In conclusion, one in five middle-aged and older adults hospitalized with COVID-19 received palliative care in our cohort. Palliative care was more likely to be implemented in patients who were very old, multimorbid, frail, and had severe COVID-19. However, we had evidence that palliative care was often delayed and did not translate into reduced utilization of advanced and invasive life support measures. With Brazil ranking among the countries with the highest number of COVID-19 cases and casualties (3), and even at times lacking ICU beds and oxygen supplies to meet the increase in demand, it would be of the utmost importance that healthcare providers be familiar with the concepts and eligibility criteria for palliative care. Front-line providers should be trained to identify palliative care candidates effectively, as well as be offered evidence-based guidelines on palliative care recommendations, ensuring rational utilization of resources while securing patient dignity and their own psychological health during the pandemic.

6. DECLARATIONS

Description of author's roles: LKR. Almeida drafted the study project, collected the data, and collaborated in writing the paper and revising it critically. Avelino-Silva TJ provided

guidance and revisions, carried out the statistical analysis, assisted with writing the paper and revising it critically. Silva DCL, Campos BA, Varela CG, Fonseca CMB, and Amorim VLP assisted with data collection. Piza FMT and Aliberti MJR guided and supervised data collection and revised the final version of the manuscript. Degani-Costa LH designed the study, drafted the study project, supervised data collection, carried out statistical analysis and assisted with writing and critically revising the final manuscript.

Research ethics and patient consent: Approval to conduct the study was granted by the Ethics Committee of Hospital Municipal Dr. Moysés Deutsch and Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAAE: 34661520.5.0000.0086). Informed consent was waived based on the retrospective and observational nature of the study, which posed minimal risk to participants. This study was performed in line with the principles of the Declaration of Helsinki.

7. REFERENCES

1.   Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

2.   Mehta OP, Bhandari P, Raut A, Kacimi SEO, Huy NT. Coronavirus Disease (COVID-19): Comprehensive Review of Clinical Presentation. Front Public Health. 2020;8:582932.

3.   COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University & Medicine: Johns Hopkins University & Medicine; [Available from: https://coronavirus.jhu.edu/map.html.

4.   Taylor L. Covid-19: Brazil's spiralling crisis is increasingly affecting young people. BMJ. 2021;373:n879.

5.   Taylor L. Covid-19: Brazil's hospitals close to collapse as cases reach record high. BMJ. 2021;372:n800.

6.   Satomi E, Souza PMR, Thome BDC, Reingenheim C, Werebe E, Troster EJ, et al. Fair allocation of scarce medical resources during COVID-19 pandemic: ethical considerations. Einstein (Sao Paulo). 2020;18:eAE5775.

7.   Ting R, Edmonds P, Higginson IJ, Sleeman KE. Palliative care for patients with severe covid-19. BMJ. 2020;370:m2710.

8.   Radbruch L, Knaul FM, de Lima L, de Joncheere C, Bhadelia A. The key role of palliative care in response to the COVID-19 tsunami of suffering. Lancet. 2020;395(10235):1467-9.

9.   Degani-Costa LH, Rolla F, Oliveira RAG, Schettino GPP, Cordioli RL, Hohmann FB, et al. Emerging from the COVID-19 pandemic: the numbers and lessons that will stay with us forever. Einstein (Sao Paulo). 2021;19:eED6207.

10.   Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95.

11.   Thomas K WJ, et al. 2016 Gold Standards Framework (GSF) Proactive Identification Guidance (PIG). 2016.

12.   Highet G, Crawford D, Murray SA, Boyd K. Development and evaluation of the Supportive and Palliative Care Indicators Tool (SPICT): a mixed-methods study. BMJ Support Palliat Care. 2014;4(3):285-90.

13.   Arcanjo SP, Saporetti LA, Curiati JAE, Jacob-Filho W, Avelino-Silva TJ. Clinical and laboratory characteristics associated with referral of hospitalized elderly to palliative care. Einstein (Sao Paulo). 2018;16(1):eAO4092.

14.   Aliberti MJR, Szlejf C, Avelino-Silva VI, Suemoto CK, Apolinario D, Dias MB, et al. COVID-19 is not over and age is not enough: Using frailty for prognostication in hospitalized patients. J Am Geriatr Soc. 2021.

15.   Lovell N, Maddocks M, Etkind SN, Taylor K, Carey I, Vora V, et al. Characteristics, Symptom Management, and Outcomes of 101 Patients With COVID-19 Referred for Hospital Palliative Care. J Pain Symptom Manage. 2020;60(1):e77-e81.

16.   Hetherington L, Johnston B, Kotronoulas G, Finlay F, Keeley P, McKeown A. COVID-19 and Hospital Palliative Care - A service evaluation exploring the symptoms and outcomes of 186 patients and the impact of the pandemic on specialist Hospital Palliative Care. Palliat Med. 2020;34(9):1256-62.

17.   Moriyama D, Scherer JS, Sullivan R, Lowy J, Berger JT. The Impact of COVID-19 Surge on Clinical Palliative Care: A Descriptive Study From a New York Hospital System. J Pain Symptom Manage. 2021;61(3):e1-e5.

18.   Smith S, Brick A, O'Hara S, Normand C. Evidence on the cost and cost-effectiveness of palliative care: a literature review. Palliat Med. 2014;28(2):130-50.

19.   May P, Garrido MM, Cassel JB, Kelley AS, Meier DE, Normand C, et al. Palliative Care Teams' Cost-Saving Effect Is Larger For Cancer Patients With Higher Numbers Of Comorbidities. Health Aff (Millwood). 2016;35(1):44-53.

20.   Janssen DJA, Ekstrom M, Currow DC, Johnson MJ, Maddocks M, Simonds AK, et al. COVID-19: guidance on palliative care from a European Respiratory Society international task force. Eur Respir J. 2020;56(3).

21.   Van Mechelen W, Aertgeerts B, De Ceulaer K, Thoonsen B, Vermandere M, Warmenhoven F, et al. Defining the palliative care patient: a systematic review. Palliat Med. 2013;27(3):197-208.

Figure 1
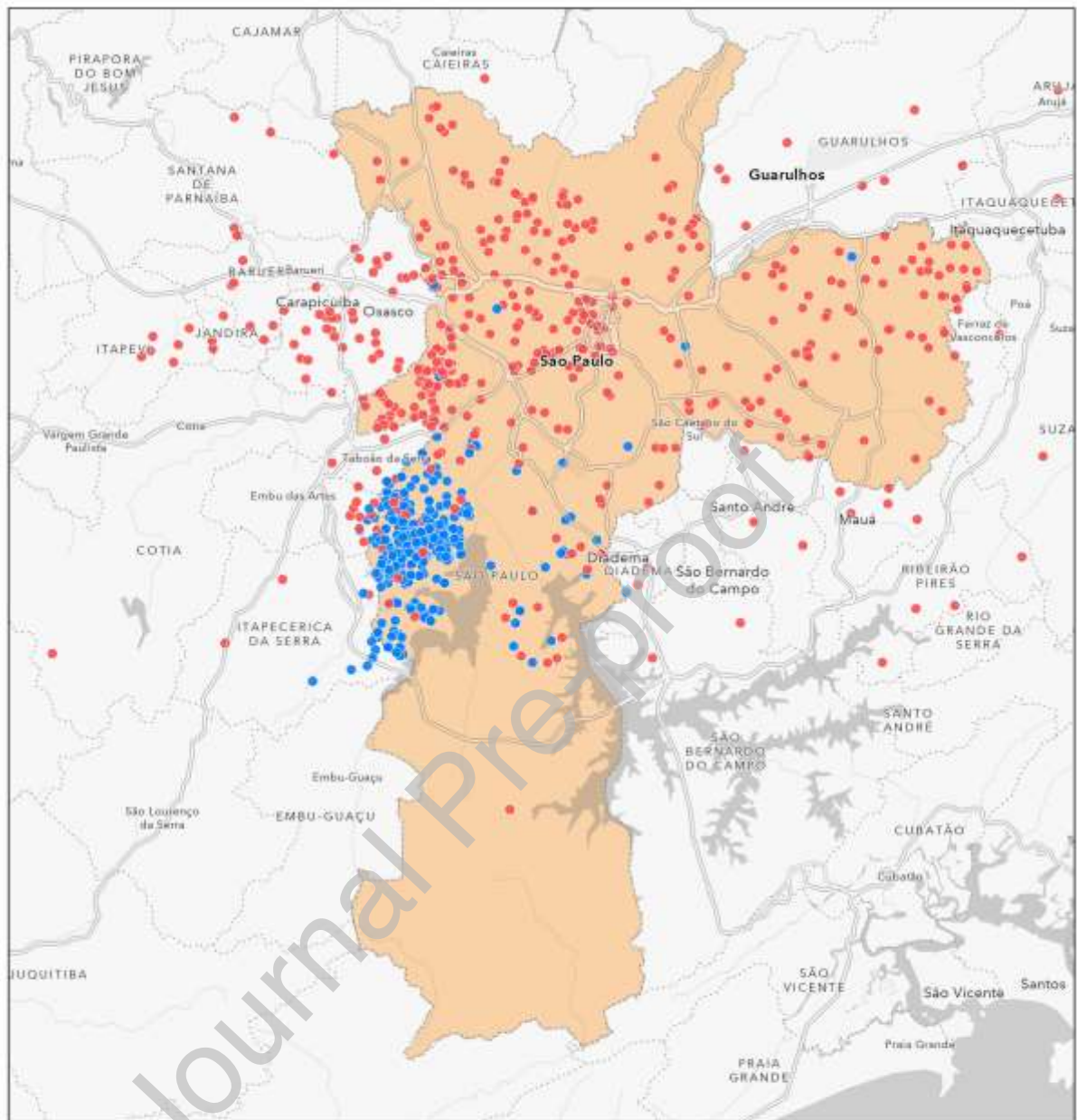
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Legend

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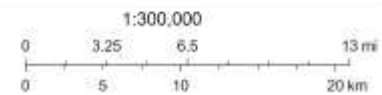
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Table 1. Participant characteristics according to study center.

	Total	Hospital 1	Hospital 2	p-value
	N=1162	N=392	N=770	
Age	65 (57 -73)	64 (56 - 72)	65 (58 - 74)	0.016
Female sex	503 (43%)	172 (44%)	331 (43%)	0.77
Asthma	46 (4%)	14 (4%)	32 (4%)	0.63
COPD	99 (9%)	34 (9%)	65 (8%)	0.89
Previous stroke	99 (9%)	26 (7%)	73 (9%)	0.10
Dementia	43 (4%)	13 (3%)	30 (4%)	0.62
Coronary disease	144 (12%)	37 (9%)	107 (14%)	0.029
Diabetes	543 (47%)	181 (46%)	362 (47%)	0.79
CKD	190 (16%)	30 (8%)	160 (21%)	<0.001
Hypertension	820 (71%)	262 (67%)	558 (72%)	0.046
Heart failure	162 (14%)	23 (6%)	139 (18%)	<0.001
Obesity	368 (32%)	86 (22%)	282 (37%)	<0.001
Cancer	127 (11%)	9 (2%)	118 (15%)	<0.001
HIV	10 (1%)	2 (1%)	8 (1%)	0.51
Smoker				0.20
Never	776 (67%)	262 (67%)	514 (67%)	
Previous	330 (28%)	117 (30%)	213 (28%)	
Current	56 (5%)	13 (3%)	43 (6%)	
Clinical Frailty Scale ≥5	247 (21%)	58 (15%)	189 (25%)	<0.001
Days of symptoms	7 (5, 10)	7 (4, 10)	7 (5, 10)	<0.001
Fever	794 (68%)	269 (69%)	525 (68%)	0.88
Cough	918 (79%)	308 (79%)	610 (79%)	0.80
Dyspnea	972 (84%)	302 (77%)	670 (87%)	<0.001
Anosmia	126 (11%)	33 (8%)	93 (12%)	0.058
Headache	200 (17%)	58 (15%)	142 (18%)	0.12
Runny nose	140 (12%)	49 (12%)	91 (12%)	0.74
Diarrhea	170 (15%)	41 (10%)	129 (17%)	0.004
Fatigue	419 (36%)	107 (27%)	312 (41%)	<0.001
Myalgia	393 (34%)	121 (31%)	272 (35%)	0.13

Corticosteroids	520 (45%)	77 (20%)	443 (58%)	<0.001
Vasopressors	236 (20%)	108 (28%)	128 (17%)	<0.001
Oxygen therapy				<0.001
None	297 (26%)	115 (29%)	182 (24%)	
Nose cannula	434 (37%)	183 (47%)	251 (33%)	
Face mask	185 (16%)	65 (17%)	120 (16%)	
Invasive ventilation	246 (21%)	29 (7%)	217 (28%)	
PaO2/FiO2	225 (123 - 285)	252 (164 - 322)	196 (105 - 246)	<0.001
CT chest scan	1010 (87%)	327 (83%)	683 (89%)	0.012
Pulmonary involvement				0.16
<25%	129 (11%)	51 (13%)	78 (10%)	
25-50%	420 (36%)	128 (33%)	292 (38%)	
>50%	461 (40%)	148 (38%)	313 (41%)	
Lymphocytes	952 (634- 1340)	1088 (774 - 1494)	890 (580 -1260)	<0.001
C-reactive protein	128 (73- 229)	114 (68 -197)	141 (77 - 240)	0.004
Length of hospital stay	11 (6, 19)	6 (3, 13)	14 (8, 22)	<0.001
ICU care	623 (54%)	132 (34%)	491 (64%)	<0.001
Most intensive oxygen therapy				<0.001
None	112 (10%)	51 (13%)	61 (8%)	
Nose cannula	405 (35%)	124 (32%)	281 (36%)	
Face mask	114 (10%)	78 (20%)	36 (5%)	
Invasive ventilation	531 (46%)	139 (35%)	392 (51%)	
Dialysis	245 (21%)	57 (15%)	188 (24%)	<0.001
Palliative care	198 (17%)	74 (19%)	124 (16%)	0.23
Death	431 (37%)	130 (33%)	301 (39%)	0.048

COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; CT = computerized tomography; ICU = intensive care unit

Table 2. Participant characteristics according to palliative care implementation.

		Palliative care		
	Total	**No**	**Yes**	**p-value**
	N=1162	**N=964**	**N=198**	
Age	65 (57- 73)	63 (56- 71)	73 (64- 81)	<0.001
Female sex	503 (43%)	401 (42%)	102 (52%)	0.010
Asthma	46 (4%)	37 (4%)	9 (5%)	0.64
COPD	99 (9%)	74 (8%)	25 (13%)	0.023
Previous stroke	99 (9%)	55 (6%)	44 (22%)	<0.001
Dementia	43 (4%)	18 (2%)	25 (13%)	<0.001
Coronary disease	144 (12%)	112 (12%)	32 (16%)	0.077
Diabetes	543 (47%)	456 (47%)	87 (44%)	0.39
CKD	190 (16%)	148 (15%)	42 (21%)	0.042
Hypertension	820 (71%)	679 (70%)	141 (71%)	0.83
Heart failure	162 (14%)	128 (13%)	34 (17%)	0.15
Obesity	368 (32%)	325 (34%)	43 (22%)	<0.001
Cancer	127 (11%)	78 (8%)	49 (25%)	<0.001
HIV	10 (1%)	8 (1%)	2 (1%)	0.80
Smoker				0.97
Never	776 (67%)	643 (67%)	133 (67%)	
Previous	330 (28%)	275 (29%)	55 (28%)	
Current	56 (5%)	46 (5%)	10 (5%)	
Clinical Frailty Scale ≥5	247 (21%)	144 (15%)	103 (52%)	<0.001
Days of symptoms	7 (5- 10)	7 (5- 10)	6 (3- 10)	<0.001
Fever	794 (68%)	675 (70%)	119 (60%)	0.006
Cough	918 (79%)	785 (81%)	133 (67%)	<0.001
Dyspnea	972 (84%)	797 (83%)	175 (88%)	0.048
Anosmia	126 (11%)	119 (12%)	7 (4%)	<0.001
Headache	200 (17%)	190 (20%)	10 (5%)	<0.001
Runny nose	140 (12%)	122 (13%)	18 (9%)	0.16
Diarrhea	170 (15%)	146 (15%)	24 (12%)	0.27
Fatigue	419 (36%)	360 (37%)	59 (30%)	0.044

Myalgia	393 (34%)	365 (38%)	28 (14%)	<0.001
Corticosteroids	520 (45%)	429 (45%)	91 (46%)	0.71
Vasopressors	236 (20%)	169 (18%)	67 (34%)	<0.001
Oxygen therapy				<0.001
None	297 (26%)	268 (28%)	29 (15%)	
Nose cannula	434 (37%)	364 (38%)	70 (35%)	
Face mask	185 (16%)	142 (15%)	43 (22%)	
Invasive ventilation	246 (21%)	190 (20%)	56 (28%)	
PaO_2/FiO_2	225 (123- 285)	242 (130- 290)	146 (108- 246)	<0.001
CT chest scan	1010 (87%)	849 (88%)	161 (81%)	0.010
Pulmonary involvement				<0.001
<25%	129 (11%)	98 (10%)	31 (16%)	
25-50%	420 (36%)	384 (40%)	36 (18%)	
>50%	461 (40%)	367 (38%)	94 (47%)	
Lymphocytes	952 (634- 1340)	970 (650- 1350)	858 (580- 1267)	0.008
C-reactive protein	128 (73- 229)	126 (71- 217)	151 (82- 273x)	0.029
Length of hospital stay	11 (6- 19)	11 (6- 19)	13 (7- 21)	0.010
ICU care	623 (54%)	498 (52%)	125 (63%)	0.003
Most intensive oxygen therapy				<0.001
None	112 (10%)	105 (11%)	7 (4%)	
Nose cannula	405 (35%)	356 (37%)	49 (25%)	
Face mask	114 (10%)	88 (9%)	26 (13%)	
Invasive ventilation	531 (46%)	415 (43%)	116 (59%)	
Dialysis	245 (21%)	194 (20%)	51 (26%)	0.077
Death	431 (37%)	261 (27%)	170 (86%)	<0.001

COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; CT = computerized tomography; ICU = intensive care unit.

Table 3. Association between participant characteristics and palliative care implementation during hospital stay.

	Univariable logistic regression			Multivariable logistic regression*		
	OR	95%CI	p-value	OR	95%CI	p-value
Demographics						
Age ≥80 years	3.31	(2.10 - 5.24)	<0.001	3.25	(2.10 - 5.04)	<0.001
Female sex	1.44	(0.99 - 2.08)	0.056			
Commorbidities						
Asthma	1.37	(0.59 - 3.19)	0.465			
COPD	1.59	(0.91 - 2.80)	0.107			
Obesity	0.59	(0.38 - 0.90)	0.015	0.60	(0.40 - 0.91)	0.016
Diabetes	0.83	(0.56 - 1.22)	0.335			
Hypertension	0.78	(0.50 - 1.20)	0.261			
Heart failure	0.80	(0.46 - 1.37)	0.410			
Coronary disease	1.29	(0.73 - 2.26)	0.382			
Previous stroke	3.34	(1.96 - 5.72)	<0.001	2.97	(1.77 - 4.98)	<0.001
Dementia	2.91	(1.37 - 6.18)	0.005	2.99	(1.43 - 6.27)	0.004
CKD	1.11	(0.69 - 1.79)	0.679			
Cancer	3.34	(2.04 - 5.47)	<0.001	3.39	(2.11 - 5.45)	<0.001
HIV	1.26	(0.24 - 6.73)	0.785			
Clinical Frailty Scale ≥5	2.68	(1.75 - 4.11)	<0.001	2.90	(1.92 - 4.36)	<0.001
Characteristics on admission						
Days of symptoms	0.98	(0.94 - 1.02)	0.320			
Invasive ventilation	1.23	(0.80 - 1.93)	0.357			
PaO2/FiO2 <200	2.35	(1.58 - 3.50)	<0.001	2.51	(1.73 - 3.63)	<0.001
Lymphocytes (cels/mm3)	1.00	(1.00 - 1.00)	0.369			
C-reactive protein ≥150 mg/dL	1.52	(1.04 - 2.23)	0.029	1.50	(1.04 - 2.16)	0.031

COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease.

* Stepwise logistic regression with backward elimination.

Table 4. Description of palliative care practice in Hospital 1.

	Indication of Palliative care*			
	Total	Multimorbidity/ Poor functional status	COVID-19 treatment failure	p-value
	N=77	N=54	N=21	
Time to initiation of palliative care (days)	8 (3 - 14)	5 (1- 11)	14 (11- 19)	<0.001
Length of hospital stay (days)	14 (8 - 26)	12 (6- 25)	16 (14- 25)	0.043
Palliation setting				<0.001
Emergency department	20 (26.7%)	18 (33.3%)	2 (9.5%)	
Ward	24 (32%)	23 (42.6%)	1 (4.8%)	
Intensive care unit	30 (40%)	12 (22.2%)	18 (85.7%)	
Invasive mechanical ventilation	45 (59.2%)	25 (46.3%)	19 (95%)	0.02
Haemodialysis	19 (25%)	6 (11.1%)	11 (55%)	<0.001
Use of vasoactive drugs	39 (51.3%)	20 (37.7%)	18 (85.7%)	<0.001
Death	61 (79.2%)	39 (72.2%)	20 (95.2%)	0.031
Time between palliation and death (days)	2 (1-6)	3 (1 – 8)	2 (1 – 3)	0.581

* Two patients were missing the reason for indicating palliative care